IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Arne Elof Brändström

Serial No. : 854,739 Examiner : J. Fan

Filed : April 21, 1986 Group Art Unit : 121

For : NOVEL COMPOUNDS

DECLARATION UNDER RULE 132

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

S I R :

I, Åke Gunnar Pilbrant, declare that:

1. I am a citizen of Sweden, residing at Snödroppevägen 6, S-434 00 Kungsbacka, Sweden.

2. I was awarded the degree of Master of Science in Pharmacy in 1965, and the degree of Farmacie Licenciat in 1969.

3. I was employed by AB Kabi, Stockholm, Sweden from 1969-1979 as Head of the Section for Development of Nonparenteral Dosage forms, Department of Pharmaceutics. I have been employed by AB Hässle, Mölndal, Sweden from 1979 to the present as Head of the Section for Product Development, Gastrointestinal Products. I am the author or co-author of about fifteen papers in the field of pharmaceutical chemistry, pharmacy, biopharmacy and pharmacokinetics.

4. I am familiar with the U.S. Patent Application Serial No. 854,739 of Brändström. I am also familiar with the U.S. Patent Application Serial No. 640,020 of Brändström, the parent application of the present application, and with the

Official Action dated January 2, 1985, in said application no. 640,020, in which the claims of the application were rejected.

5. I have executed a Declaration under Rule 132 in the said application no. 640,020.

6. I have caused a number of tests to be run to compare the stability of base addition salts of omeprazole with neutral omeprazole under two different storage conditions.

7. Sodium, calcium and magnesium salts of omeprazole were prepared according to the method described in U.S. Patent Application Serial No. 640.020. Samples of these salts, and of neutral omeprazole were placed in amber glass bottles, sealed with snap-cap polyethylene closures, and stored at 50°C. A second set of samples were placed in open petri dishes and stored at 37°C and 80% relative humidity.

8. Samples were withdrawn from each test container at time zero, and after 1, 3 and 6 months of storage. Magnesium and calcium salts were analyzed after 1.5 months rather than 1 month of storage.

9. The withdrawn samples were made into solutions containing 0.12 mg/ml of omeprazole by extraction with 25.0 ml of ammonia-methanol solution (6.0 ml conc. ammonia diluted to 100 ml with methanol) diluted to 1 liter with methylene chloride. The solutions were analyzed by HPLC using the extraction solvent as the mobile phase to determine the amount of degradation products.

10. Degradation of omeprazole was determined from the amount of degradation products (by-products) formed and shown in the Table for each of the compounds tested.

The Table gives the total amount of by-products

found after storage of omeprazole in neutral form for a given period of time, compared with the total amount of by-products formed after storing of the sodium, magnesium and calcium salt of omeprazole.

It is the stability data obtained after long term storage, that is after at least six months, that constitute the essential result of the tests.

It is seen in the Table that after six months storage, the neutral omeprazole test substance contains more than 4 (test at 50°C) and more than 6 (test at 37°C and 80% relative humidity) percent by-products. By contrast, the amount of by-products after six months in the tested omeprazole salt preparations ranges in the test at 50°C from 0.1% (the sodium salt) to 1.1% (the calcium salt), and the amount of by-products at six months in the test at 37°C and 80% relative humidity ranges from 0.7 (the magnesium salt) to 1.7 (the calcium salt). Thus, the amount of by-products formed in neutral omeprazole after six months is at least 4 times (4:1.1) higher than in the tested salts, in the test at 50°C, as well as in the test at 37°C and 80% relative humidity (6:1.7).

11. The seemingly inconsistent test results in the Table after storage for 1(1.5) and 3 months may be explained by the following factors:

a) Differences in surface reactivity.

Omeprazole substance was crystallized from an organic solvent system and dried. In order to increase the surface area of the substance it was micronized (mean particle size about 3 µm) in an air jet milling apparatus. The milling makes the powder cohesive and also renders it a very hydrophobic surface.

Omeprazole calcium salt was prepared by reacting one equivalent of omeprazole substance with approximately one half equivalent of anhydrous calcium chloride in water. The precipitate was collected, washed, dried and milled. This procedure gives particles which have a hydrophilic surface.

When these two substances are exposed to an accelerated storage condition of 37°C, 80% relative humidity they react differently with regards to water absorption.

Omeprazole micronized substance with its hydrophobic surface reacts slowly and it takes quite some time before water has been adsorbed to the total surface, where it can fully exert its effect on the degradation of omeprazole.

Omeprazole calcium salt with its hydrophilic surface adsorbs water rapidly which starts a degradation reaction at once. This applies also to the tested sodium and magnesium salts.

b) The tested substances are not totally pure initially, which might influence the stability. The substances were tested by liquid chromatography and UV-detection. The sum of impurities and degradation products was calculated assuming the same molar absorbtivity as omeprazole. The small differences in the sum of by-products, obtained at low levels, must therefore be regarded as less significant compared to the differences obtained after six months.

Consequently, a comparison of the long term storage stability of these substances should be based on results obtained after at least 6 months of storage. A real difference in stability between omeprazole and the salts is seen after six months of storage as shown in the Table. The

enclosed chromatograms (Figures 1 and 2) show omeprazole after 1 and 6 months at 37°C and 80% relative humidity and omeprazole calcium salt initially and after 6 months at the same conditions. All chromatograms are evaluated using the same scale expansion. It is obvious that the chromatogram of omeprazole contains significantly more and larger by-peaks compared with the chromatogram of the calcium salt after 6 months of storage.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent thereon.

Dated: July 11, 1986

Åke G. Pilbrant

ÅKE GUNNAR PILBRANT

Table

Total amount of by-products found after storage of omeprazole and omeprazole salts. The results are given as percent of intact omeprazole (peak area percent)

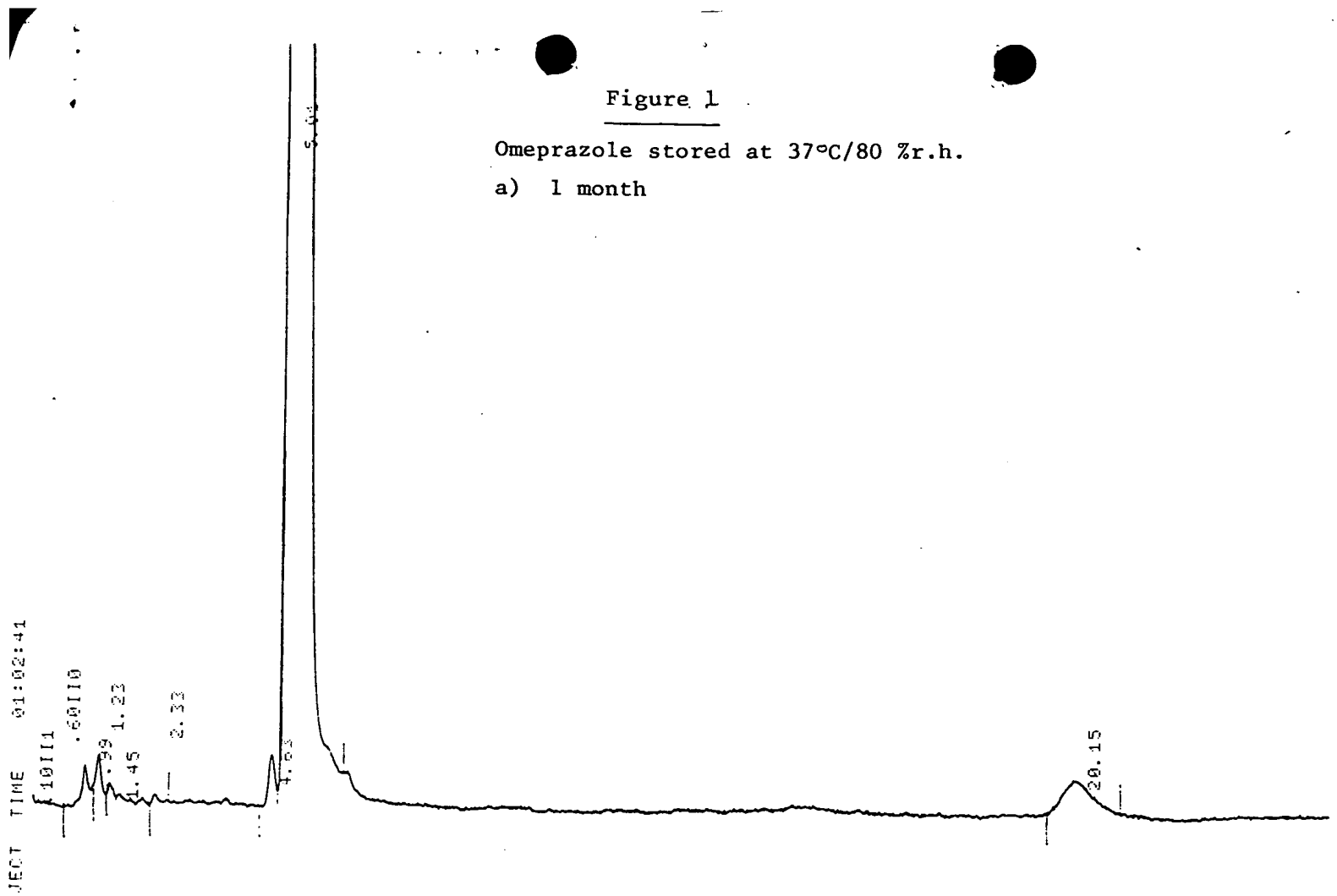
Storage time, months	Storage conditions °C/% r.h.	Omeprazole	Omeprazole sodium salt	Omeprazole magnesium salt	Omeprazole calcium salt
0	-	0.2	0.1	0.2	0.2
1*	+50	0.2			
	+37/80	0.2	0.1	0.3	1.5
3	+50	1.0	0.1	0.4	0.9
	+37/80	0.3	0.8	0.4	1.7
6	+50	>4	0.1	0.6	1.1
	+37/80	>6	1.2	0.7	1.7

*The magnesium and calcium salts were analysed after 1.5 months storage.

Figure 1

Omeprazole stored at 37°C/80 %r.h.

a) 1 month



b) 6 months

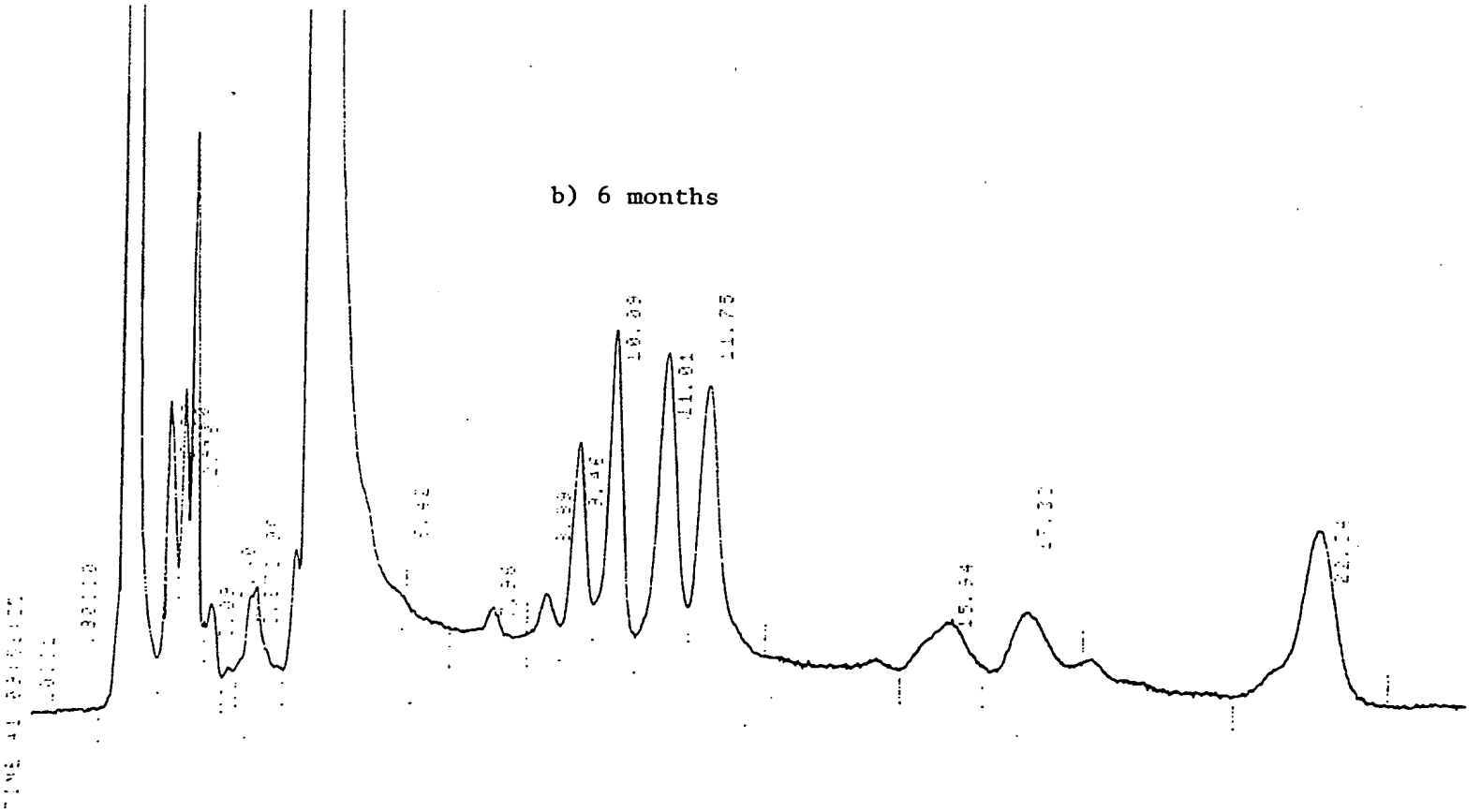
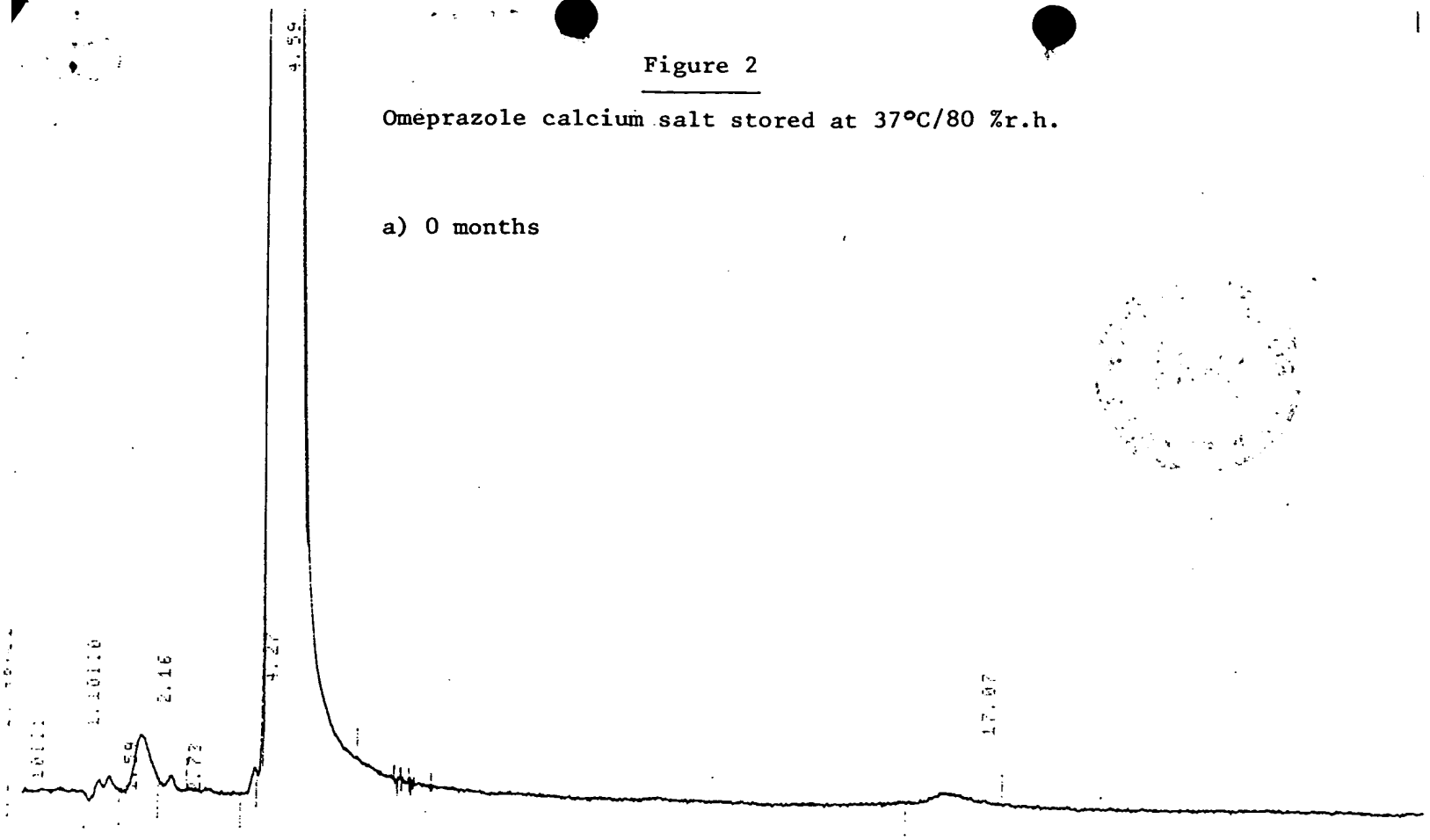


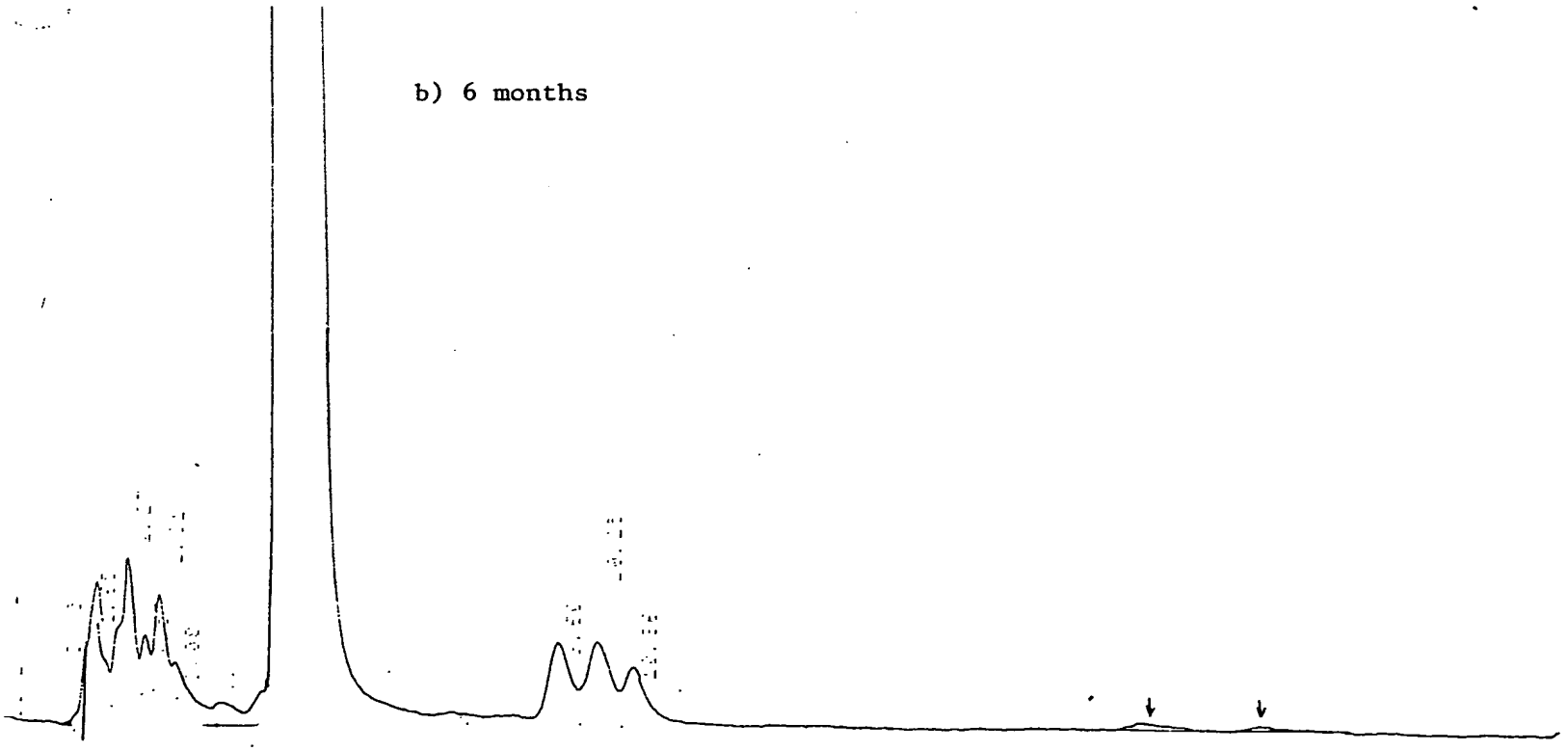
Figure 2

Omeprazole calcium salt stored at 37°C/80 %r.h.

a) 0 months



b) 6 months



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